REMARKS

Claims 33-51 are pending. These claims stand rejected as being obvious over U.S. Patent No. 4,073,922 to Wyburn-Mason, in view of ADAP Drugs, the PDR Electronic Library, and U.S. Patent No. 6,545,028 to Jensen. The Office previously acknowledged that the specification provides data demonstrating synergistic inhibition of TNF-α secretion by the combination of an azole and steroid *in vitro*. The Office nonetheless states (page 6) that "a showing of unexpected results *in vitro* cannot overcome a rejection of obviousness in the case here where the breath of the claim includes the treating of a patient."

Applicants respectfully disagree with the Office's contention that unexpected results *in vitro* cannot overcome an obviousness rejection when the claims encompass treating patients. The synergistic inhibition of TNF-α by a steroid and an azole *in vitro* do predict a similar therapeutic effect in a treated patient given precedents set by numerous studies of TNF-α, consistent with the guidelines prescribed by the MPEP. According to the MPEP 716.02(d), "the objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." The objective evidence of nonobviousness presented by the invention, namely the invention's *in vitro* activity detailed in the specification, is commensurate in scope with the claims directed to treating patients.

As is discussed in greater detail below, the *in vitro* results provided by Applicants necessarily extend to treated patients, because (1) TNF-α is directly implicated in

rheumatoid arthritis, and (2) FDA-approved inhibitors of TNF-α, originally identified *in vitro*, have proved therapeutic effect in rheumatoid arthritis patients.

Various lines of evidence establish a relationship between the inhibition of TNF-α and rheumatoid arthritis. For example, TNF-α overexpression correlates to rheumatoid arthritis and TNF-α is found overexpressed at the sites of inflammation. Elevated levels of TNF-α have been detected in the joints of mice with collagen-induced arthritis (CIA); CIA is ameliorated or prevented with anti-TNF antibodies; and inflammatory arthritis has been shown to develop in transgenic mice overexpressing TNF-α. TNF-α is also found in high concentrations in the rheumatoid joint.

Furthermore, drugs that inhibit TNF-α are already used to treat rheumatoid arthritis. Three TNF inhibitory agents approved by the U.S. Food and Drug Administration as of 2003 for the treatment of rheumatoid arthritis are infliximab (Remicade), a chimeric monoclonal antibody that binds TNF-α and TNF-β (lymphotoxin-α), etanercept (Enbrel), a human TNF receptor protein dimer fused to human IgG1 that binds TNF-α and TNF-β, and adalimumab (Humira), a fully human anti-TNF-α antibody. Etanercept and infliximab were approved for the treatment of rheumatoid arthritis on Nov. 2, 1998 and Nov. 15, 1999, respectively. On Oct. 4, 2005, the FDA approved adalimumab for first-line treatment of recent onset moderate to severe rheumatoid arthritis.

Each of these approved drugs has its origins in studies *in vitro* demonstrating its activity. Infliximab specifically binds to both soluble and membrane-bound TNF-α with high affinity ($Ka = 10^{10} M^{-1}$). Knight et al. (*Mol. Immunol.* 30:1443-1453 (1993))

demonstrated that the binding of infliximab (referred to in Knight et al. as cA2) to TNF-α prevents the binding of TNF-α to its receptors and blocks the initiation of the intracellular signaling that leads to gene transcription and subsequent biologic activity (exhibit 1). Murray et al. (*Ann. Pharmacother.* 31:1335-8 (1997)) demonstrated that etanercept (referred to in Murray et al. as TNFR:Fc) binds to and inactivates TNF-α with a high binding affinity and is a potent inhibitor of TNF-α activity *in vitro* (exhibit 2). Kempeni (*Ann. Rheum. Dis.* 59(suppl I):i44-i45 (2000)) demonstrated that adalimumab (referred to in Kempeni as D2E7) inhibits binding of human TNF-α to its p55 and p75 receptors on human cells and is highly selective for TNF-α (exhibit 3). By comparison, the combination of an azole and a steroid reduces the amount of TNF-α that is secreted. Although the mechanism differs from that of the anti-TNF-α protein therapeutics that act by binding TNF-α, both methods have the same effect of reducing "free" TNF-α. Therefore, given the clinical success of the anti-TNF-α therapeutics, the clinical benefits of the combination of an azole and a steroid are predicted.

In further support of Applicants' position that the synergy observed in *in vitro* studies should be sufficient evidence to overcome the rejection of the claims for obviousness, Applicants note that, in co-owned U.S. Application No. 10/264,991, another drug combination demonstrated to have *in vitro* synergy was also shown to have *in vivo* synergy in a rat model of rheumatoid arthritis. In a declaration submitted in the aforementioned application (attached herewith as exhibit 4), Applicants demonstrated that a combination of dipyridimole and prednisolone, which synergistically inhibits TNF-

α production *in vitro*, similarly shown to reduce clinical manifestations of rheumatoid arthritis in rats synergistically. Moreover, this combination of dipyridimole and prednisolone has shown to be effective in humans (see exhibit 5).

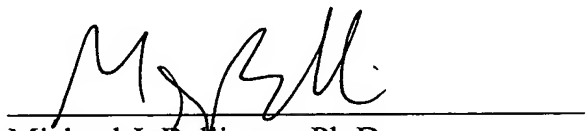
Because other agents that effectively reduce free TNF-α are effective in treating rheumatoid arthritis, a practitioner would reasonably expect the claimed combination—shown to have synergistic *in vitro* activity—would also have synergistic *in vivo* activity. For this reason, Applicants respectfully request that the rejection of the claims as being obvious be withdrawn.

Conclusion

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the final Office action for two months, to and including November 15, 2006, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 11/15/06



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